

SURGERY AND DIABETES MELLITUS

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Summary:-

The relationship between surgery and diabetes mellitus is examined, principally in terms of the diabetic patient who is subjected to operation. However, account is also taken of situations where diabetes may be precipitated or, indeed, treated by surgical intervention.



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Surgery and Diabetes Mellitus

Although diabetes mellitus is regarded primarily as a medical condition, it has wide-ranging implications for the surgeon especially in terms of the diabetic patient undergoing a surgical procedure.

In addition, it is becoming increasingly evident that surgery may have an important role in the treatment of the disease and its complications, and to facilitate discussion of this extensive subject the essay will be divided into 3 sections:-

1. Complications and Management of Diabetes Mellitus in the Surgical Patient.
2. Surgery and Surgical Conditions Precipitating Diabetes Mellitus and related metabolic disorders.
3. Treatment of Diabetes Mellitus and its complications by Surgery.

1. Complications and Management of Diabetes Mellitus in the Surgical Patient.

Regardless of the reason for operation, the diabetic patient presents a special challenge not only because of the impairment of glucose and lipid metabolism and the consequent effect on electrolyte and fluid balance, but also because of dysfunction in the vascular tree, the immunological system and the wound healing process. It is therefore essential that diabetes is not "palmed off" on to the medical side but is treated as an integral part of the surgical condition so that an optimal state for operation is achieved.

i) Surgery as a potential diabetogenic stimulus.

Any patient undergoing surgery faces 3 stress situations - anxiety, anaesthesia, and surgical trauma; in the diabetic patient this combination may lead to metabolic decompensation.

Anxiety stress causes sympathetic stimulation and release of corticosteroids and adrenaline adding to the similar effect of surgical stress on these factors.

Anaesthesia certainly raises blood sugar, especially when chloroform or ether is used, but the observed rise is only 10 - 50 mg/100 mls (Steinke 71), and the choice of general anaesthetic is not influenced by the presence of diabetes mellitus (Galloway 67, Shipp 68). However, anaesthetic management should be designed to cause minimal stress and to be rapidly reversible so that the patient may be fed orally as soon as possible. A general anaesthetic should therefore be as "light" as possible to allow a rapid return to consciousness with little nausea and vomiting. Local anaesthetic is the method of choice when feasible and elderly patients may even undergo amputation with spinal anaesthesia (Marble 63); the consequent sensory denervation may even have positive value in atherosclerosis as it causes peripheral vasodilation, but a careful watch must be kept for the arterial hypotension which follows sympathetic denervation (Greene 67). Pre-operative medication should be kept to a minimum as diabetic patients, especially the elderly, are often sensitive to narcotics and sedatives and the inherent danger of respiratory-depressed hypercarbia, hypoxia and acidosis is exaggerated (Marble 63). Morphine also causes/

causes release of ACTH (Johnston 73) and should thus be avoided as glucocorticoids are markedly diabetogenic.

Surgical trauma is the greatest compromising factor in this trio and the degree of stress, as measured by elevated blood sugar, depends on the duration and magnitude of the procedure; intraabdominal manipulation seems to be the most stressful situation (Clarke 70). What is "stress" and how does it elevate blood sugar and precipitate diabetic coma in the susceptible patient? The answer to this question, as far as we can answer it, is a multifactorial one. As already suggested, nervous and endocrine mechanisms play a central role in the stress reaction. The common factor is probably any painful stimulus, especially that arising from traction on the viscera, which transmits impulses centrally to the spinal cord and midbrain causing reflex secretion of the appropriate hormones, even under profound anaesthesia. It is significant that ACTH and cortisol levels do not rise in injury to paraplegic limbs and are delayed and reduced in spinal anaesthesia (Johnston 73). The hormones concerned have a complex, interacting effect on metabolism and it is best to consider them in turn.

Adrenaline rises markedly during major surgery due to sympathetic stimulation of the adrenal medulla and remains high well into the recovery phase. This stimulates glycogenolysis, decreases glucose uptake in muscle, inhibits pancreatic insulin release and stimulates glucagon release and mobilises free fatty acids due to activation of triglyceride lipase.

Cortisol levels rise during surgery as a result of ACTH release. Owing to this gluconeogenesis is increased, glucose uptake in adipose tissue is decreased and free fatty acids are mobilised by the activated lipase. It is now considered that the metabolic implications of adrenocortical secretions in the post-operative period are small (Johnson 73) but in the diabetic patient glucocorticoids may be a major factor in decompensation.

Glucagon also rises in response to surgery, due to a combination of nervous sympathetic stimulation of the pancreas and the releasing effect of circulating adrenaline. This stimulates liver gluconeogenesis and glycogenolysis and again mobilises free fatty acids by an action on the triglyceride lipase.

Growth Hormone/

Growth Hormone levels tend to rise in the post-operative stage; this stimulates gluconeogenesis, decreases glucose uptake by adipose tissue and mobilises free fatty acids. The hormone is also thought to release somatomedin from the liver which antagonises insulin by binding to receptors on the fat cell membrane.

Insulin secretion during surgery is reduced but in the first few days after the operation there is a paradoxical increase and high levels of insulin are found at a time when glucose metabolism is still impaired. At this time many insulin antagonists are present - adrenaline, cortisol, glucagon, GH and sympathetic stimulation of the pancreas itself. The insulin rise is probably due to hyperglycaemia and to the effect of glucagon; this may explain poor glucose uptake in the face of high insulin levels (See pseudo-diabetes). In addition a traumatic cell membrane defect may result in a certain degree of insulin resistance (Johnston 73). Insulin, of course, is the hypoglycaemic hormone, increasing glucose uptake in all tissues save brain and red blood cells, inhibiting glycogenolysis, gluconeogenesis and lipolysis, and stimulating glycogen synthesis.

Thus the actions of these hormones under the stimulus of trauma is to precipitate hyperglycaemia and, to a lesser extent, ketosis (See diagrams 1 and 2). If this happens in the normal patient, then the diabetic will be in dire straits, as his metabolic tendencies are already in this direction due to a relative or absolute insulin deficiency. It is therefore mandatory that the patient's metabolic condition be kept as stable as possible around the time of surgery.

ii) Electrolyte and Fluid Imbalances of the Diabetic State and their dangers.

Having examined the mechanism of metabolic decompensation in response to surgical trauma it is now appropriate to look at the effects of this process and the ways in which they endanger the patient. The changes are similar to those seen in uncontrolled diabetes, where the precipitating factor is insulin lack, but during and after surgery they are more likely to occur, as has been discussed above.

Diabetic coma, as the state of metabolic decompensation is called, consists of two major conditions - hyperglycaemia and ketoacidosis (See diagrams 1 and 2). Hyperglycaemia produces an osmotic diuresis which may bring about dehydration and hypovolaemia with peripheral circulatory collapse. Due to its presence in the ECF, the osmotically active glucose also causes intracellular loss of water which leads to severe degrees of tissue dehydration and electrolyte imbalance. In addition, if/

if there is a marked insulin deficit, lipase disinhibition and diminished intracellular glucose utilisation will result in an overwhelming mobilisation of fatty acids from adipose tissue with the development of ketoacidosis (See diagram 2).

These two conditions have great effects on electrolyte balance, and it is important to consider these defects - especially with regard to sodium, potassium and phosphate.

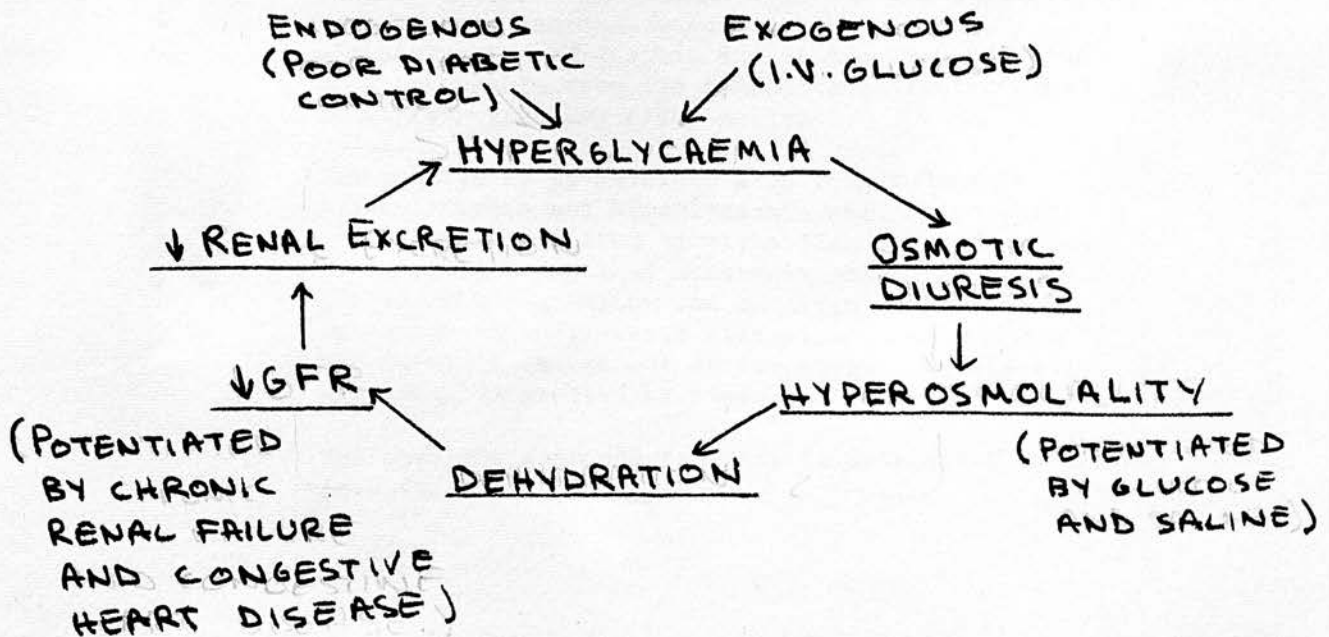
Sodium balance - plasma sodium falls due to glucose in the ECF producing an osmotic effect which moves water out of the cellular compartment diluting extracellular solutes; for every 100 mg/ 100 mls increase in blood sugar there is a 1.6 mEq/l fall of plasma sodium (Katz 73). The total level of sodium in the body is reduced by the loss of water and sodium by the diuresing kidney. Hyponatraemia as a clinical entity is manifested by cramps, confusion, weakness and convulsions.

Potassium balance - total body potassium falls because of the osmotic diuresis and because of the increased levels of aldosterone brought about by hypovolaemia and hyponatremia. Aldosterone promotes retention of sodium at the distal tubule and excretion of potassium. However, in acidosis due either to ketosis or lactic acidosis in response to poor tissue perfusion, plasma potassium may rise, as H^+ ions are exchanged for K^+ across the cell membrane. Insulin deficiency also plays a part as this hormone has been shown to promote the cellular uptake of potassium. There may thus be a state of potassium depletion but no demonstrable hypokalaemia, and this calls for careful consideration of potassium balance while correcting metabolic decompensation. Replacement of potassium too early may cause hyperkalaemia, whereas excessively vigorous treatment with insulin and/or bicarbonate may precipitate a dangerous hypokalaemia due to migration of K^+ ions into the cells. Clinically, hyperkalaemia causes cardiac arrhythmias; hypokalaemia decreases renal ability to concentrate and may also precipitate cardiac failure.

Phosphate balance - in hyperglycaemia there is urinary loss of phosphate as glucose and phosphate compete for tubular reabsorption (Pitts 44) - low phosphate levels decrease cerebral function and may cause/

cause weakness, tremors, haemolysis and poor platelet function. In addition 2-3 DPGA levels in red blood cells are reduced in uncontrolled diabetes due both to phosphate depletion and to a specific action of low pH (Alberti 72). This causes an increased affinity of haemoglobin for O_2 (i.e. the O_2 dissociation curve is shifted to the left). Acidosis, on the other hand, shifts the curve to the right and in diabetic acidosis it is thought that 2-3 DPGA is important in the homeostasis of the red blood cells. However, if the acidosis is corrected too rapidly, the low 2-3 DPGA levels cannot keep pace with the rising pH in the face of phosphate depletion and this results in decreased delivery of O_2 to the tissues which may already be compromised by poor perfusion. It has accordingly been suggested that fluid regimens for the treatment of diabetic ketoacidosis should include phosphate and exclude bicarbonate (Alberti 72).

Although this sequence of events is the commonest form of decompensation, there is another related condition which arises in elderly patients with mild late onset diabetes. This is termed hyperosmotic non-ketotic diabetic coma (Libertino 70) and is characterised by hyperglycaemia, hypernatremia, dehydration and increased serum osmolality. Ketoacidosis is absent although lactic acidosis is common. The syndrome is precipitated or exacerbated by surgery because of an endogenous or exogenous glucose load which cannot be handled physiologically at the cellular level. The endogenous load is stress-related and the exogenous load may result from fluid therapy with dextrose without insulin. Chronic renal insufficiency and congestive heart disease are often present concomitantly and these conditions may potentiate the "vicious circle" which results :-



The hypernatraemia may be explained by the fact that in a precipitous osmotic diuresis H_2O is lost to a greater extent than Na^+ , although why this should cause hypernatraemia exclusively in this syndrome is not clear; it is more likely that exogenous administration of saline along with the dextrose is a causative factor. Absence of ketosis is probably due to the pancreas being able to secrete physiologically active levels of insulin.

At this stage it is worth mentioning a condition which is severely compromised by the presence of diabetes mellitus - namely prostatic obstruction. After the relief of urinary retention there is normally a post-obstructive uropathy with profuse solute diuresis (Moore 63). The solute load and the tubular disease, both of which are caused by the chronic obstruction, cause a severe diuresis due to the blockage of water reabsorption. In diabetic hyperglycaemia, which may be exacerbated by the surgical procedure, the soluble diuresis is greatly increased. Sodium loss is considerable, but much more water is lost as sodium is reabsorbed by the tubule so that hypotonicity, hypernatraemia and severe dehydration result. Renal tubular acidosis also complicates the picture. Energetic fluid management must therefore be applied to counteract this until the tubules have recovered, and careful diabetic management must be instituted before the operation.

iii) Management of the diabetic surgical patient with regard to potential metabolic decompensation.

It must be stressed that these metabolic changes are due to diabetogenic surgical stress processes being superimposed on the insulin-deficient diabetic state and, in the normal patient, decompensation will not readily occur. Accordingly, if the diabetic patient is kept in a "normal" condition by judicious administration of insulin and fluids, he should have no more trouble from the immediate metabolic upset of surgery than any other patient.

The problem is to maintain a balance between hyperglycaemia and hypoglycaemia and, as we shall see, this is achieved by withholding the endogenous hypoglycaemic agent to a certain extent so that a limited sugar infusion can be given during the operation which prevents starvation ketoacidosis but is small enough not to compromise the diabetic exacerbation created by stress.

The specific approach can only be determined by taking account/

account of the individual's diabetic status and the severity of the surgical procedure. It therefore behoves us to consider the surgical management of the various manifestations of diabetes under separate headings:

- a) The Known Diabetic
 - 1. late onset, diet-controlled
 - 2. late onset, on oral hypoglycaemic agents
 - 3. insulin dependant.
- b) The Undiagnosed Diabetic.
- c) Emergency Surgery in Diabetes.

a) The Known Diabetic

If a patient requiring elective surgery is known to be a diabetic, there are certain precautions which can be taken regardless of the nature of his disease. He should be admitted 1 - 2 days in advance for evaluation of his condition; this must include blood and urine glucose levels, OGTT, blood Na^+ , K^+ , total CO_2 , ketoacids and urea. Haemocrit and state of hydration should also be examined.

If there is any degree of decompensation due to poor control or to some other factor such as an abscess, this should be corrected by appropriate fluid and insulin therapy. Cardiac and respiratory systems should be carefully examined, as in all patients, and the extent of any vascular disease ascertained. Renal function should also receive careful scrutiny especially if high urea levels are detected.

On the day of surgery, a fasting blood sugar is obtained as a baseline, no breakfast is given and a slow intravenous infusion of 1000 mls 5% dextrose started to prevent starvation ketoacidosis. Post-operatively a second blood glucose must be taken to check that the balance between hyperglycaemia and hypoglycaemia has been maintained. On this basic framework, the following refinements may be hung according to the type of diabetes:

1. The Late onset diet-controlled Diabetic Patient.

The non-insulin dependant diabetic who is well controlled by diet alone can usually get by on the surveillance outlined above. If, however, the diabetic state deteriorates in the post-operative period, insulin may be temporarily required. A single daily subcutaneous injection of 10 - 20 units of isophane (NPH) or lente insulin is usually suitable (Steinke 71). The fear that **once** a patient takes insulin he must always take insulin has not been substantiated; when the patient has recovered/

recovered insulin can usually be discontinued, especially if the surgery has removed the reason for decompensation (eg. an abscess). Although in general the single dose of insulin is suitable, a sliding scale technique is commonly used to try to obtain a more precise control. This consists of the administration of short acting soluble insulin according to four hourly urine sugar levels. A typical sequence would be - 15 units of soluble insulin subcutaneously for a 4+ specimen, 10 units for a 3+ specimen, 5 units for a 2+ specimen and none for 1+ or less. The amount of insulin needs to be adjusted individually - that is, it may be reduced for an elderly, cachectic patient and increased for an obese patient.

The sliding scale technique certainly has its advantages, as insulin requirements tend to fluctuate after an operation. A major surgical procedure may necessitate a sharp increase in insulin dosage, but during convalescence insulin requirements tend to return to pre-operative levels or even lower if a decompensating factor such as an abscess or an inflamed gall bladder has been removed, and thus hypoglycaemia may be precipitated if insulin dosage is not tailored accordingly (Arky 71). However, the disadvantage of estimating insulin dosage on the basis of urine sugar are threefold. First of all, it requires frequent urine collection. Secondly, it assumes a normal renal threshold, but with age the renal threshold often increases and, as a result, the patient may be undertreated. Finally, the insulin treatment is always several hours behind the blood sugar, and thus the sliding scale technique does not anticipate the need for insulin but rather prescribes it retrospectively. It is therefore probably better, if the sliding scale is to be employed, to give a small prophylactic dose of NPH insulin, supplemented if necessary by soluble insulin.

While discussing late onset, non-insulin dependant diabetes, the phenomenon of hyperosmotic non-ketotic coma must not be omitted. The commonest cause of this condition is the administration of large amounts of glucose and saline to post-operative diabetics with impaired renal function. It is important to note that 5% dextrose and saline is the normal fluid replacement in post-obstructive diuresis, and in diabetes this therapy should be avoided. If coma should develop, the following therapeutic regime has/

has been suggested (Libertino 70). Soluble insulin 50 units intravenously and 50 units subcutaneously should be given and fluid therapy carried out with 2 litres of $\frac{1}{2}$ normal saline and 2.5% fructose given rapidly in a drip. Fructose has the advantage of being used intracellularly in the absence of insulin and $\frac{1}{2}$ normal saline soon replaces the sodium and water lost in the glucose-induced diuresis. Subsequent therapy consists of insulin every 2 hours until the blood glucose is less than 300 mg/100 mls, at which time 5% dextrose can be started intravenously and the fructose-saline discontinued. It is also noteworthy that thrombotic phenomena have been suggested as complicating hyperosmotic coma (Hobin 73) and anticoagulant therapy may have a place. However, this was an isolated report and the association may have been co-incidental.

2. The Patient on Oral Hypoglycaemic Agents.

If the surgery is minor, the tablets should be omitted pre-operatively and given before supper if short acting (tolbutamide) or withheld until the next day if of the long acting type (Chlorpropamide). However, if the procedure is an extensive one, a switch to insulin is usually made. This is indicated if major surgery is planned, if general anaesthetic is indicated, if intravenous feeding is required for several days or if the diabetes is poorly controlled. The insulin can be administered on a sliding scale or as a small subcutaneous injection of intermediate insulin daily as before, and this should be continued until oral intake is recommended. It has recently been suggested that intravenous tolbutamide may be more effective than insulin in these cases (Schmitt 68) but an extensive comparison of the two methods is not yet feasible.

3. The Diabetic Patient on Insulin.

Operations on an insulin dependant diabetic should be scheduled early in the morning so that the period of fasting is not prolonged. No subcutaneous insulin should be given after the evening meal on the night before and, of course, no foods or liquids should be taken after midnight both to prevent hyperglycaemia and for anaesthetic considerations. Although/

Although most diabetics are maintained on intermediate insulin which will have worn off by the day of surgery, it must be ascertained that a long-acting variety has not been given. On the day of operation, the total insulin dosage should be reduced (usually by $\frac{1}{3}$) because of the limited glucose intake and the danger of hypoglycaemia.

When minor surgery is to be performed, and if oral intake can be resumed in the evening, insulin should be withheld until the patient is in the recovery room when $\frac{2}{3}$ of the total dose is given. In this way hypoglycaemia is avoided and hyperglycaemia is unlikely because of previous fasting and the low stress level of the operation.

In major surgery, however, when diabetogenic stress processes are exaggerated, it is better to give $\frac{1}{3}$ of the total insulin dosage before the operation and $\frac{1}{3}$ after to be supplemented in the post-operative period by soluble insulin on a sliding scale if necessary. For example, if the normal dose of insulin is 15 U soluble and 35 U NPH every morning, then the patient should receive 5 U + 12 U subcutaneously as a 5% dextrose infusion is started pre-operatively. In the recovery room, another 5 U + 12 U should be given and his urine monitored for sliding scale administration of soluble insulin for the rest of the day. If on the next day intravenous fluids are to be continued, insulin can again be administered $\frac{1}{3}$ in the morning and $\frac{1}{3}$ in the afternoon, adjustments being made on the basis of fasting and 3 p.m. blood sugars. Once the patient has been returned to oral feedings, insulin can be resumed in a single injection. However, blood sugar monitoring must be continued until it is certain that the patient's insulin requirements have stabilised.

It should be mentioned that some prefer to withhold all insulin on the day of surgery until the post-operative period when it is administered only by the sliding scale technique so that hypoglycaemia is avoided. However, the combination of the slow glucose infusion and the metabolic effects of anxiety, anaesthesia and surgery will counterbalance the effects of the pre-operative insulin and, in practice, hypoglycaemia is uncommon. If hypoglycaemia does occur, it may well be that the patient has been on an/

an unrestricted diet with large amounts of insulin, and when a calorie controlled diet is administered in hospital the insulin requirement is not adjusted.

Up to this point only the subcutaneous administration of insulin has been advocated. However, some workers feel that insulin should only be given intravenously both pre and post operatively, until 100 gm of carbohydrates can be taken orally, when subcutaneous administration can be recommenced (Greene 67). They also suggest that only soluble, short-acting insulin should be used around operation. The rationale is that subcutaneous insulin, even if soluble, has a more lingering effect than intravenous and thus cannot be so readily controlled, especially on the basis of urine sugars. However, I feel that if the pre-operative medication is limited to soluble intravenous insulin, the combination of dextrose infusion and a long, stressful operation may precipitate hyperglycaemia and present difficulties in the post-operative fluid management.

It will be noticed that the verbs "feel" and "suggest" have been prominent in the above discussion and this exemplifies the subjective nature of diabetic management in the surgical situation. To be quite honest, it is neither possible nor particularly desirable to maintain rigid control of diabetes during surgery and it must be remembered that overtreatment in the pre or post operative period is more dangerous than mild occasional hyperglycaemia and glycosuria. As long as an intelligent approach to diabetes is maintained, the specific mode of treatment is of little account.

b) The Undiagnosed Diabetic Patient.

A mild diabetic may be so well compensated as to escape detection, but under the stress of surgery develop hyperglycaemia and ketoacidosis leading to dehydration and electrolyte loss. Ideally, this should never happen as all patients admitted for surgery should be screened for diabetes. If hyperglycaemia or glycosuria are detected, surgery should be postponed until the diabetic state has been evaluated by an OGTT and perhaps a cortisone OGTT. It must be remembered that the presence of sugar in the urine does not always indicate diabetes mellitus. Renal glycosuria, in which there is a low renal threshold for glucose, does not require treatment but these patients do have sugar in their urine and therefore easily develop starvation ketosis when fasted. Thus they may exhibit glycosuria and ketonuria and may be indistinguishable from true diabetics if only urinary findings are taken into account.

c) Emergency Surgery in Diabetes.

If the patient is in a reasonable state of diabetic control, emergency surgery may be carried out almost immediately. A brief/

brief diabetic history, a urine test for sugar, acetone and protein, a blood sugar determination, a plasma acetone test and blood tests for bicarbonate, electrolytes and urea determinations suffice for a rapid diabetic evaluation.

On the other hand, if the diabetes is uncompensated, either because it was unknown or because of underlying disease such as a severe infection, it must be controlled especially if acidosis is present and this usually necessitates a delay of 4 - 5 hours. Of course, in cases of uncontrolled haemorrhage, respiratory insufficiency or raised intracranial pressure, which are surgically correctable, operation should proceed immediately and the patient treated for coma on the table.

The treatment must be directed at three objectives - rehydration, restoration of electrolyte balance and restoration of acid-base balance. The amount and type of fluid will vary with the patient's condition. If there is severe dehydration with good cardiac and potential renal function, 4 - 6l of normal saline are indicated. If, however, cardiac or renal function is poor, a less than normal saline infusion should be given; with severe hyponatraemic non-ketotic coma, in an emergency it may be best to omit sodium altogether and use 5% dextrose despite the hyperglycaemia. Total body potassium will probably be low as well, but it must be remembered that because of the acidosis and insulin lack, plasma potassium may be normal or even high. It is therefore necessary to wait until potassium levels start to drop before administering it in the infusion. If intravenous bicarbonate is used for the rapid correction of ketoacidosis and for lactic acidosis, it must be used with extreme caution as a too rapid correction of acidosis may precipitate a dangerous hypokalaemia. It may also be justified to add phosphate to the intravenous fluid to compensate for the urinary loss which occurs in the hyperglycaemia. Efficient therapy depends on frequent blood sampling and estimation of blood glucose, plasma (K^+) and total CO_2 , and a foley catheter should also be employed as restoration of urinary output dictates the total amount of intravenous water required. The amount of insulin required varies with the blood sugar, timing of the last insulin injection and the magnitude of the surgical procedure. None may be required until the post-operative period or, if the blood sugar is raised the usual daily dose may be given pre-operatively. If the patient is ketoacidotic it is best to give 50 units intravenously and 50 units subcutaneously to be repeated every two hours if indicated by laboratory tests.

Before concluding this section on diabetes and emergency surgery it is important to mention that diabetic ketoacidosis may mimic an abdominal emergency such as acute/

acute appendicitis (Steinke 70). Indeed this may be the presentation of diabetes in childhood and give a picture of abdominal pain and vomiting with an increase in blood sugar and decreased bicarbonate. However, such a picture may be due to, say, acute appendicitis with consequent decompensation of previously undetected diabetes. It is often impossible to come to a diagnosis at the outset and the situation is best treated with insulin and fluids before attempting laparotomy.

iv) Other Complications of Diabetes Mellitus relating to the Surgical Patient.

1. Infection.
2. Wound Healing.
3. Myocardial Dysfunction.

1. Infection.

It is well documented that diabetics are particularly susceptible to infection (Lipscomb 59, Thornton 71, Koota 70, Younger 65) and this of course has important implications in surgery. Wound infections have been reported as being four times as common in diabetics than in a normal population (Koota 70) and urinary tract infection is a common ailment. How much of the latter is due to depressed bactericidal activity in the diabetic bladder mucosa and how much to prolonged catheterisation is not clear (Lipscomb 59) but a careful watch must be kept for bacturia, as pyelonephritis or even a fatal gram negative septicaemia may develop. Staphylococcal and streptococcal skin infections are often seen in diabetics (Thornton 71), especially in areas of vascular insufficiency, and these may well give rise to a bacteraemia or septicaemia.

Why do diabetics have a propensity for developing infections? There are various proposed reasons, all of which may contribute to the total explanation. Bacteria do not appear to grow more quickly in diabetic blood (Cruickshank 54) and so the rather simplistic view of hyperglycaemic blood as a good culture medium is not generally accepted. Furthermore, it has been demonstrated that gamma-globulin levels are essentially normal, suggesting that a failure of the humoral immune response is not a major factor (Lipscomb 59). It must be mentioned, however, that a delay in the attainment of maximal antibody titres was noted after injection of staphylococcal toxin (Bates 41) and so B- lymphocytes May be slightly compromised in diabetes. Certainly physiological levels of insulin enhance lymphocyte-mediated cytotoxicity (Strom 75) and hypoinsulinaemia may well be responsible for suboptimal lymphocyte responsiveness.

Impairment of neutrophil function has also been observed in patients with diabetes mellitus, although there is much debate as to the aetiology. The early granulocyte phase of the local cellular/

cellular response was shown to be delayed in acidotic patients only (Perillie 62) and in another study phagocytic activity in neutrophils was depressed, again uniquely in acidosis (Bybee 64). However, other work has indicated that the antimicrobial action of neutrophils was markedly reduced in non-ketotic patients and that the defect was strongly related to hyperglycaemia (Bagdade 74). This study did not distinguish between phagocytosis and intracellular killing, but both functions have been shown to be depressed separately, using the lysostaphin technique (Tan 71, Tan 72). To confuse matters further, defective neutrophil function in diabetic patients has also been noted independent of ~~ketosis~~ acidosis and hyperglycaemia (Tan 72). As several of the key enzymes required for glucose metabolism in neutrophils are insulin dependant (Klebanoff 71) and as phagocytosis depends on glucose metabolism, insulin deficiency could well be implicated in the dysfunction.

Thus we have a rather equivocal picture; it is possible that acidosis, hyperglycaemia and insulin deficiency combine to render neutrophil function less than adequate but, of course, there may be an even more basic defect in the diabetic polymorph which is as yet undetected.

Vascular insufficiency is also a major factor when considering susceptibility to infection. Poor perfusion due to atherosclerosis is common, especially in the distal extremities, and this is almost certainly the most important reason for the frequency of leg and foot lesions in the diabetic. In addition, capillary clearance and end-vessel reactivity to pressor substances are delayed in diabetes mellitus (Mullane 70) and this may also compromise resistance to infection.

What special precautions then must be taken with a view to minimising the danger of infection in a diabetic patient undergoing surgery? As in all patients, there must be a scrupulous observation of aseptic technique, and many surgeons avoid the use of diathermy, preferring to tie all vessels in one hope of minimising any perfusion deficit which may occur. Prompt drainage of any localised septic process is vital, especially in areas of ischaemia where systemic antibiotics are of little use and, in such cases, topical antibacterial substances may be indicated (Moore 63). When a septicaemia develops, this calls for aggressive antibiotic treatment based, ideally, on blood culture sensitivity studies, but therapy should be started immediately and changed if necessary when the bacteriological reports/

reports are returned. Prophylactic antibiotics are also strongly indicated when a limb is to be amputated. Recently, a group of workers have applied local insulin to infected burns in diabetes (Hoshi 73) but although the results were promising no controlled study has yet been done.

2. Wound healing

The tensile strength of healing abdominal wounds has been shown to be reduced in rats rendered diabetic with alloxan, especially when the diabetes was poorly controlled (Rosenthal 62). This was histologically related to decreased wound content of collagen and delayed formation of granulation tissue (Shah 74); at this point the well documented neutrophil dysfunction should be remembered. Although it is always dangerous to extrapolate from animal models to human subjects, special care should nevertheless be taken when suturing wounds in diabetic patients, and removable sutures should perhaps remain in place longer than usual. A possible delay in fracture healing is another feature noted in diabetics (Cozen 72) although this is not well documented.

3. Myocardial Insufficiency

Any myocardial dysfunction must always be taken into account when considering the management of the surgical patient. Diabetics are particularly susceptible to this, not only as a result of atherosclerosis but also because of the high levels of FFA which are now thought to depress myocardial function by raising Acetyl CoA levels which in turn inhibits transfer of ATP from the mitochondria (De Levis 75, Rowe 75).

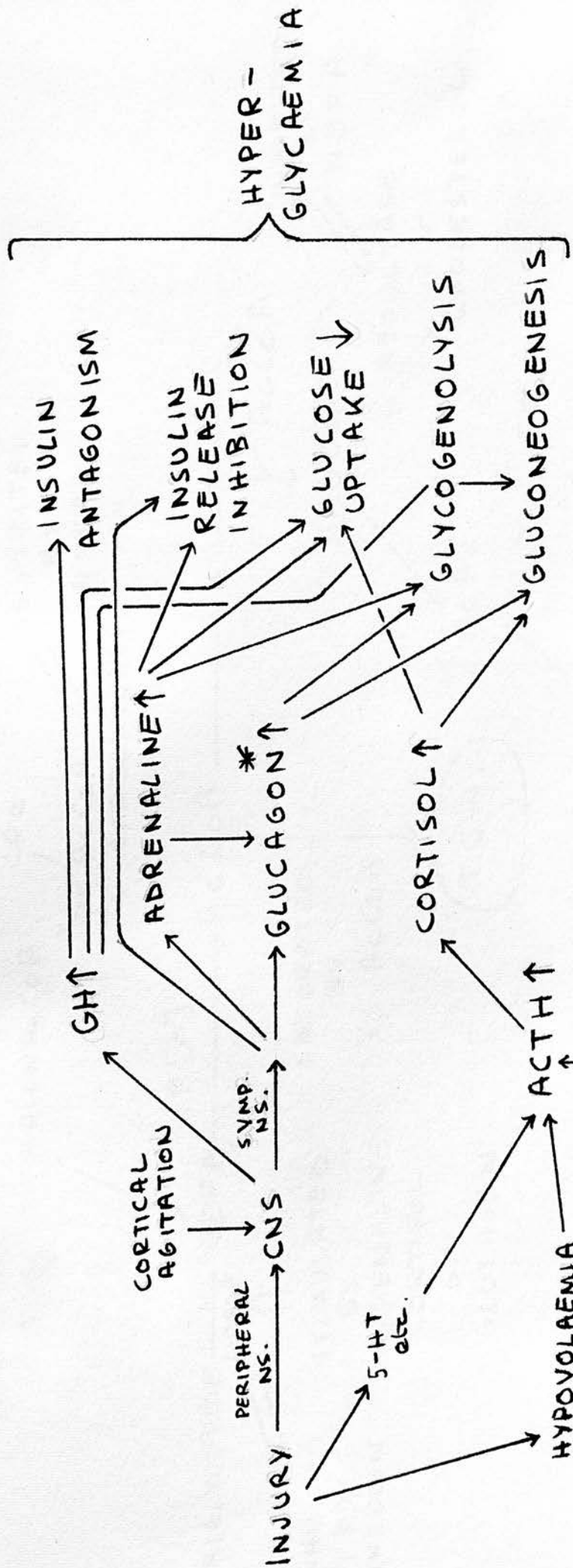
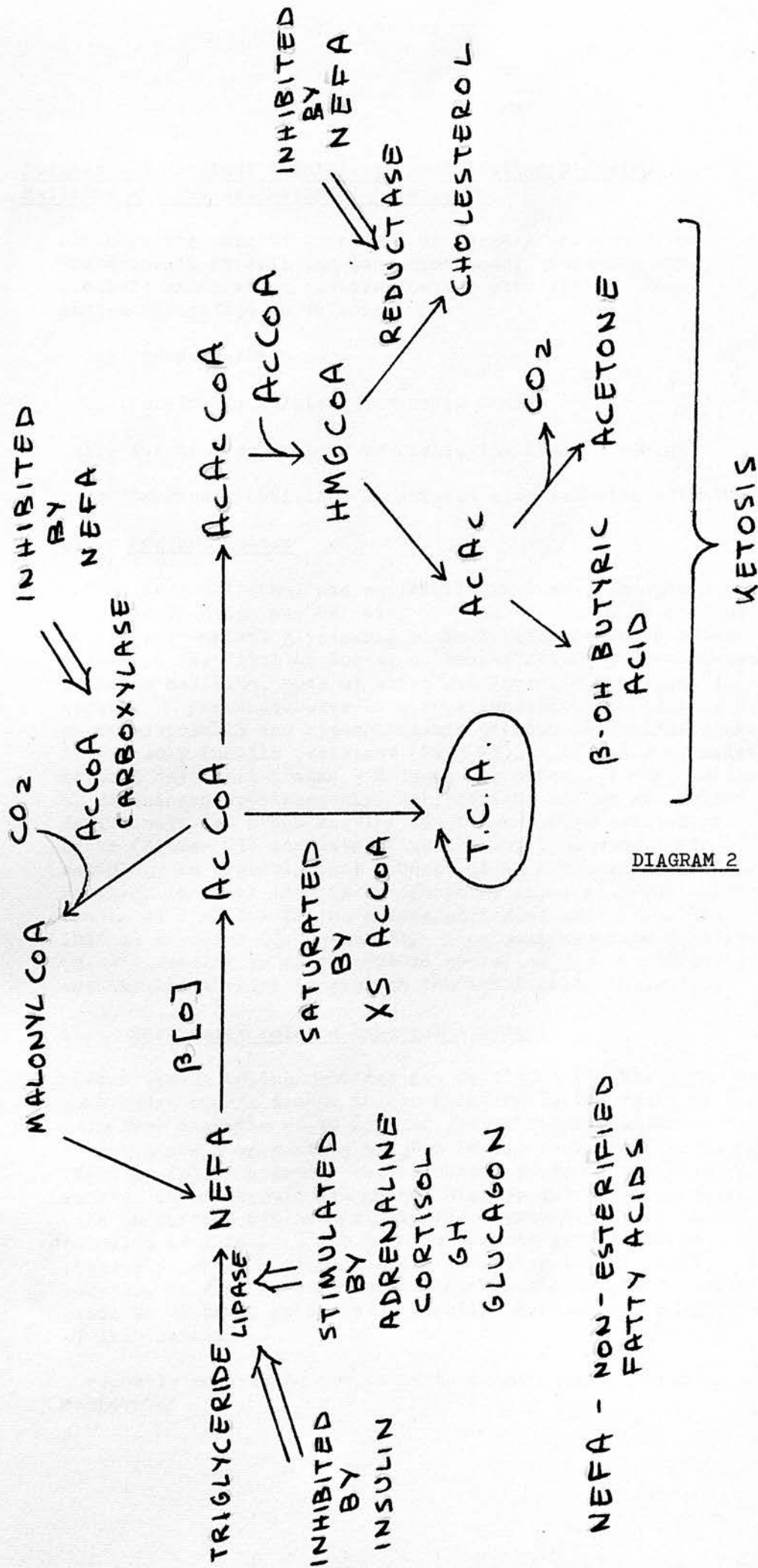


DIAGRAM 1

* NOTE THAT GLUCAGON STIMULATES THE RELEASE OF INSULIN



2. Surgery and Surgical Conditions Precipitating Diabetes Mellitus and Related Metabolic Disorders.

Although the important concept of surgery and trauma as diabetogenic stimuli has been discussed, there are some specific areas which require further scrutiny. These may be classified as follows:

- i) Pseudodiabetes
- ii) Surgically related pancreatic damage
- iii) Surgical conditions precipitating hypoglycaemia
- iv) Surgical conditions associated with diabetes mellitus.

i) Pseudodiabetes

In any severe trauma, and especially in burns, the phenomenon of pseudodiabetes may be seen. This is not to be confused with the transient glycosuria without ketouria which often occurs in the first 48 hours, or exacerbation of pre-existent diabetes mellitus, both of which are "normal" reactions to stress. Pseudodiabetes is a rare condition, consisting of gross glycosuria and hyperglycaemia without ketoacidosis which is markedly insulin resistant (Muir 73). It tends to arise several days post-trauma and lasts for several weeks; although it diminishes spontaneously, dehydration, sodium and potassium deficiency, and gross wasting due to excessive catabolism occur (Stoner 73) and fatalities are not uncommon. The aetiology is probably best thought of as a supranormal stress reaction in which insulin antagonists, especially adrenaline, remain at high levels for a long period of time after the initial stimulus (Johnston 73). Treatment consists of high calorie feeding in an attempt to spare the protein catabolism, and insulin therapy to protect the islet cells (Muir 73).

ii) Surgically related pancreatic damage.

Direct trauma to the pancreas and carcinoma of that organ may both cause enough damage to the islet cells to create an insulin deficient diabetic state (Stoner 73). Indeed, diabetes mellitus is sometimes a presenting symptom in pancreatic carcinoma (Webster 75). However, the commonest cause of diabetes related to pancreatic damage is total or subtotal pancreatectomy. This is carried out not only in the treatment of carcinoma, but also to alleviate the pain in chronic pancreatitis; when contemplating such drastic measures in the latter condition, however, it must be remembered that the alcoholic is particularly prone to diabetic acidosis or insulin overdosage during periods of inebriation.

A recently documented series of total pancreatectomies for malignant/

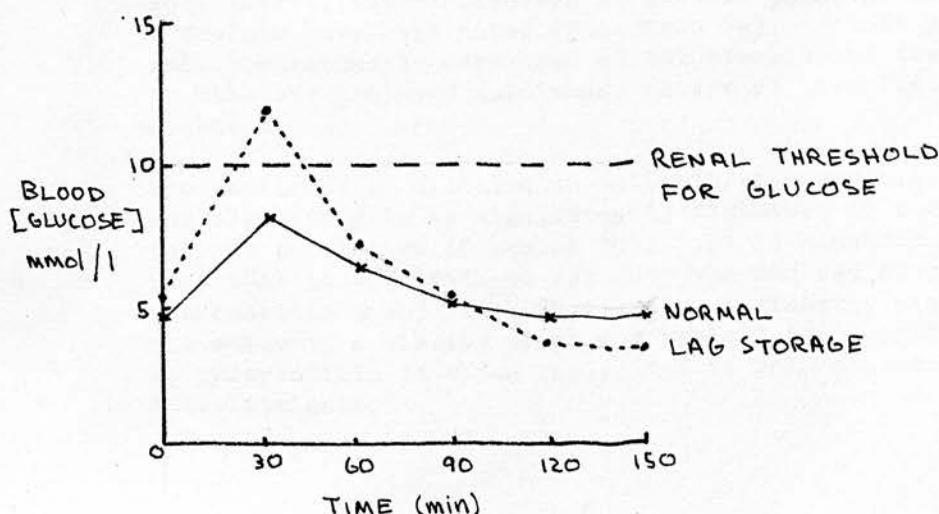
malignant tumours from 1942-1973 has indicated that 76% of the patients were easily managed with conventional insulin treatment whereas only 24% developed brittle poorly controlled diabetes (Pliam 75). This is perhaps not surprising as there can be no residual insulin secreting capacity to complicate matters. Another interesting finding from this study is that diabetic neuropathy, nephropathy and retinopathy were not major problems in the long term status of these patients. In fact, only 7% developed retinopathy and 13% neuropathy and all the long term complications only occurred in the earlier section of the group. In addition, the only patient with severe retinopathy was a known diabetic for a long time before pancreatectomy. This raises the question of whether the long term complications of diabetes are related to insulin deficiency and its sequelae at all, but are perhaps due to some other basic defect. There is also the possibility that, with the whole pancreas gone, the diabetes is more easily and more effectively controlled due to the absence of any indeterminate and perhaps fluctuating insulin secreting capacity. It may seem far fetched, but would juvenile diabetics benefit from total pancreatectomy? The answer is that this series is too small and that not enough patients have survived for a sufficient time to carry out the extensive long term follow up which would be required before significant conclusions could be drawn.

iii) Surgical conditions precipitating hypoglycaemia.

Hypophysectomy and adrenalectomy in the diabetic patient are operations which require careful post-operative management. As both operations tend to remove insulin antagonists - ACTH and GH in the case of the pituitary, and cortisol and adrenaline with the adrenals - the patient is rendered hypersensitive to insulin. As a result, insulin must be administered cautiously and in very small doses. In this context, it is worth noting that in acromegaly, diabetes mellitus develops in about 25% of cases due to the antagonistic effects of GH, and surgical hypophysectomy is often the treatment of choice.

Another operation which gives rise to disorders of carbohydrate metabolism, this time in the non-diabetic patient as well, is partial or total gastrectomy. Due to the loss of the "resevoir" function of the stomach, immediate post prandial hyperglycaemia is frequently seen, often accompanied by glycosuria, and without adequate knowledge a diagnosis of diabetes mellitus might be entertained. However, the hyperglycaemia has a characteristic/

characteristic course which is best illustrated by an OGTT



This is known as "lag storage". Note that although the $\frac{1}{2}$ hour glucose is abnormally high, the 2 hour value is lower than usual, and the relative hypoglycaemia is caused by the hyperinsulinaemia precipitated by the transient hyperglycaemia. This hypoglycaemia may give rise to some symptoms 2 - 3 hours after a meal, and has been termed "delayed dumping". The treatment is similar to the management of hypoglycaemia in early juvenile diabetes and consists of the reduction of the amount of simple sugars in the diet and replacement by slowly absorbed starches and sugars in small frequent feedings (Arky 71). Anticholinergic agents may also be useful as rapid gastric emptying is an important aetiological factor in the subtotal gastrectomy problem.

Pregnancy, although not strictly a surgical condition, is also worth considering at this stage. A pregnant diabetic woman requires large amounts of insulin due to insulin resistance caused by placental hormonal factors such as corticosteroids and H.P.L. When the baby is delivered, these factors disappear and insulin requirements drop immediately to pre-pregnant levels. It is therefore wise to reduce the dose of insulin by about a half on the day of delivery, or to omit the usual insulin altogether and work on the sliding scale principle. If, for some reason, the normal dose of insulin has been given, the mother should be covered by an intravenous infusion of 10% glucose; occasionally 50% "pushes" in the form of intravenous injections may be required to prevent or treat severe hypoglycaemia.

iv) Surgical conditions associated with diabetes.

There are some surgical conditions which are associated with diabetes although their relationship with the disease is not clear. Dupuytren's contracture is one (Gunther 72), and another is carcinoma of the stomach (Forgacs 73). Atrophic gastritis is frequent in diabetics and/

and, indeed, auto-antibodies to gastric parietal cell cytoplasm have been noted (Robertson 74); this may well predispose to carcinoma of the stomach and ties up with the proposed autoimmune nature of juvenile diabetes.

The incidence of diabetes in patients with cholelithiasis was also found to be significantly higher than in a normal control population (Schmauss 70). It is significant to note that in 40% of these patients who had had severe pancreatitis 3 - 5 years previously, a diabetic disorder was evident, a finding which may explain the association, as pancreatitis is often implicated in both diabetes and cholelithiasis.

3. Treatment of Diabetes Mellitus and its complications by Surgery.

Finally we must consider the role which surgery has to play in the treatment of the complications of diabetes and its potential in the therapy of the actual disease itself. To facilitate discussion, it is convenient to look at each complication separately:

- i) Vascular Disease.
- ii) Renal Disease.
- iii) Retinopathy.
- iv) Pancreatic Transplantation.

i) Vascular Disease.

Quite apart from microangiopathy, which is thought to be related to basement membrane deficiencies, diabetics are prone to atherosclerosis. Aldose reductase is present in the aorta, and thus high glucose levels produce a metabolic change within the wall, which may combine with hyperlipidaemia to produce atherosclerosis in the large vessels (Clements 69).

This predisposition gives rise to vascular insufficiency, especially in the lower extremities, which may call for surgical intervention. Unfortunately, amputation is often the only course open to the surgeon and, in general, the healing rate after an above-knee amputation is greater than that for mid-leg. However, preservation of the knee is of considerable benefit for the efficient use of a prosthesis, and it is of great importance to amputate as low as possible but without creating a wound which will not heal. Some authors consider that the amputation level is best determined by skin temperature and appearance alone, rather than relying on pulses and arteriography (Echer 70). Different sources, however, hold the X-ray techniques in great esteem (Tolstedt 61) and it is thought that a below-knee amputation is unlikely to heal if the superficial femoral artery is found to be blocked at the adductor hiatus, or if the superior geniculate artery is not patent.

The outlook is not always so bleak, however, and gangrene in the foot of a diabetic may not have amputation as its inevitable outcome if careful clinical evaluation is carried out (Williams 74). Foot gangrene develops not only because of a poor blood supply but also because the patient is often unaware of minimal damage, owing to his peripheral neuropathy. It must be impressed on patients with neuropathy that careful foot hygiene and early consultation are of the essence, and if this is carried out the prognosis is considerably better.

Foot lesions may be classified into three groups on the basis of the clinical findings. Firstly, there is necrosis in the cold foot. This is due to serious arterial insufficiency, necrosis starting/

starting as distal gangrene which may become infected later. In this case, major amputation is the inevitable result. Secondly, necrosis in a hot foot indicates that the arterial circulation is good and the condition usually develops as a localized traumatic ulcer which becomes infected. Necrosis results from the direct effect of bacterial toxins and the consequent thrombosis in small vessels. Local excision and preservation of part of the foot is possible in most cases, and the wound should be left open to heal by granulation with skin grafting later if necessary. The third presentation is necrosis in a warm foot in which there is a proximal block of the arterial system, with good collateral circulation. Gangrene starts with an infection necrosis, but relative ischaemia hinders localisation. Arterial surgery may be successful but this is more useful before necrosis starts. Local excision should be attempted as healing will occur in 50% of cases (Williams 74). Lumbar sympathectomy has no place in the treatment of necrotic lesions of the foot, but when the foot has healed it may be valuable in making it more resistant to damage.

When major blood vessels have been blocked, usually by a combination of atheromatous plaque and thrombus, arterial surgery may have therapeutic effects if the distal vasculature is not extensively involved. Thrombendarterectomy in which the thrombus and intima are removed through an incision in the vessel wall is often employed if the blockage is not extensive. However, femoropopliteal saphenous bypass grafts are more effective when there is a large occlusion at the femoral and popliteal arteries, and when the blockage involves the aorta and iliac vessels, a Y-graft of dacron or some similar material is often the best measure. It must always be borne in mind that selection of patients is important if useful results are to be achieved, and claudication is a more hopeful presentation than necrosis or rest pain (Stipa 71).

ii) Renal Disease

Diabetic nephropathy is thought to be due to an enzyme-mediated deposition of carbohydrate units in the basement membrane of glomerular capillaries which is active in insulin deficiency (Spiro 73). However, even well-controlled juvenile diabetics often develop glomerulonephritis and even have to be put on chronic dialysis for which there is a high mortality and a tendency for neuropathy and retinopathy to deteriorate (Leading Article 75). When the diabetes is relatively uncomplicated in terms of peripheral vascular disease, severe blindness, or peripheral neuropathy, kidney transplantation is often a more satisfactory treatment, especially if the donor is a living relative. However, graft survival is less in diabetics than in non-diabetics, and much poorer results are obtained when cadaver kidneys are used. Urological complications are commoner in diabetics after transplantation and a neurogenic bladder may be a lethal complication because of intractable infection. Reversal of the remaining complications does not usually occur after renal transplantation although there is a suggestion that visual acuity tends to stabilise; gastro-intestinal symptoms generally improve suggesting/

suggesting that they are mostly uraemic in origin.

There is still no evidence that transplanted kidneys develop diabetic abnormalities; basement membrane thickening does occur in long-term survivors, but it is not known whether this is a diabetic change or a consequence of transplantation. Rejection phenomena are similar to those seen in non-diabetics, although it should be noted that insulin requirements usually rise following transplantation owing to the large doses of steroids given for immunosuppression (Beaudry 73). Taking into consideration the fact that the diabetic with renal insufficiency will deteriorate rapidly, and the finding that retinopathy may advance more quickly as renal function declines, it may be justifiable to consider transplantation in diabetics at an earlier stage than normal, despite the lower success rate of the operation.

iii) Retinopathy.

Diabetic retinopathy can be divided into two stages - "exudative" or "Background" and "proliferative". The first type, which occurs earlier in general, and is less severe, consists of microaneurysms with associated dot haemorrhages, hard exudates, and macular oedema. The more severe proliferative retinopathy develops later and is characterised by neovascularisation, preretinal haemorrhage and increased proliferation of connective tissue. The pathogenesis of these conditions is not understood, although basement membrane changes similar to those seen in glomerular capillaries have been implicated. The surgical treatment of retinopathy takes three forms - photocoagulation, hypophysectomy and vitrectomy.

Photocoagulation can be directed against both background and proliferative retinopathy, and is carried out using a xenon arc, a ruby laser or an argon laser. Light energy from a xenon arc is directed at the retina where it is absorbed forming a discrete scar and areas of neovascularisation or bleeding are coagulated and prevented from further extension (Baladimos 70). It is also useful in the treatment of background retinopathy, where the mechanism is probably related to the cauterisation of capillaries (Multicentre Trial 75). The ruby and argon laser are employed in a similar fashion, but they are also used to create 500 - 1000 scars throughout the retina, sparing the disc, macula and maculopapular bundle. This, theoretically, alters the course of proliferative retinopathy by occluding capillaries which supply the new vessels, or by reducing the overall metabolic requirement of the retina and hence the demand for vascular supply (Merin 71). The argon laser (green light) is thought to be superior to the ruby laser (red light) for destroying new vessels because of the better absorption of green light by red haemoglobin. Two controlled studies have been carried out on the use of the xenon arc (Multicentre Trial 75) and the argon laser (Patz 73) for the treatment/

treatment of macular oedema in background retinopathy. In both cases the conclusion was that the treatment delays the deterioration of diabetic maculopathy, but that the difference between treated and untreated eyes did not increase with longer follow-up. This suggests that photocoagulation slows or stops the retinopathic process for a time, but that it then proceeds at its old pace. It was also noted that the prognosis was at its best in those with a visual acuity of $\frac{6}{24}$ or better (Multicentre Trial 75) and accordingly photocoagulation should be considered before retinal damage is too advanced. As yet no controlled trials indicating the usefulness of photocoagulation in proliferative retinopathy have been carried out.

Hypophysectomy is another, more drastic, treatment for retinopathy and is reserved for severe, progressive proliferative disease with impending blindness when at least one macula is salvageable. Why this procedure should have any effect is unknown, although it may be related to the elimination of ACTH and GH, both of which aggravate diabetes (q.v.). The techniques are various, but the transsphenoidal approach with selective microsurgical anterior pituitary ablation is becoming the most popular. The results are generally quite good; in 64 - 88%, stability or improvement of visual acuity is achieved with clearing of vitreous opacities, involution and disappearance of new vessels, resolution of retinal oedema and a decrease in venous calibre (Balodimos 71). However, the advantages of such a major procedure have to be weighed against the considerable disadvantages. For a start, in a proportion of patients relapse occurs after a few years, and in all subjects adrenal, thyroid and gonadal insufficiency necessitate exogenous replacement therapy. Insulin requirements generally fall by about 50% but insulin sensitivity becomes extreme and the diabetes becomes brittle and hard to control. Because this technique is reserved for almost hopeless cases, its efficacy is hard to evaluate. It is impossible, for example, to conduct a comparison of the results with those of photocoagulation which is used in the much earlier stages of retinopathy. However, if hypophysectomy could be shown to bestow a significantly better prognosis than other techniques, it might be justifiable to subject relatively young people to hormonal mutilation in order that their eyesight might be preserved.

Vitrectomy, in which the whole vitreous is removed except a relatively thin layer lying on the retina, is rarely done in diabetes. Its main use is the removal of severe vitreous haemorrhage which is unlikely to resorb, but in diabetes, recurrent haemorrhage is the likely course of/

of events (Stallard 68). Nevertheless, the operation has recently been employed with a degree of success in the elimination of pre-retinal traction bands which tend to cause retinal detachment and in the removal of vascular proliferations (Machemer 75).

iv) Pancreatic Transplantation

At the present time the major, if not the basic defect of diabetes mellitus appears to be insulin deficiency. The value of surgery in the treatment of this factor is extremely limited, but there are some procedures which may prove useful in the overall management of juvenile onset diabetes. Recently, bilateral solarectomy and ligation at the middle and inferior suprarenal arteries has been reported as being helpful in insulin resistant diabetes (Chapo 74), presumably by partially removing the insulin-antagonistic effects of adrenaline and cortisol. However, this operation has not been widely employed and is not well documented, so judgement must accordingly be delayed. On the other hand, there is an extensive literature relating to pancreatic transplantation, a procedure which holds out a certain amount of hope for the treatment of insulin dependant diabetes where the pancreas is dysfunctional. As far as attempts to use this technique on humans is concerned, however, the procedure is still at a very early stage, and most of the work described below has been done on dogs.

Early efforts to obtain endocrine function with non-vascular implants of pancreatic tissue were disappointing (Reemtsma 68) and so all recent attempts at total or subtotal transplantation have included vascular reconstruction. Thrombosis is a major complication of the operation, partially due to the tortuosity of the pancreatic vasculature, and partially because the exocrine portion is highly sensitive to trauma and is prone to release proteolytic enzymes. It is therefore necessary to avoid diminished venous return from the grafted organ, and this is best done by end to side venous anastomoses; arterial inflow does not appear to be a complicating factor (Pennel 69). Apart from the common factor of vascular anastomoses, the techniques for transplantation are widely varied, but two major methods can be described. Firstly, there is the pancreaticoduodenal graft, in which the donor's pancreas is transferred along with its attached duodenum (De Jode 66, Merkle 68, Kelly 67, Idezuki 68, Largiader 67, Lillehei 70); the piece of gut is then either included in the recipient's gastrointestinal tract, or is exteriorised at one end and used as a conduit for exocrine secretions. The major disadvantage of this method is the severe effect of acute rejection on the duodenal segment, when it displays extensive haemorrhage and ulceration (Kelly 67, Merkel 68). Whether this is because bowel is particularly antigenic, or whether it is merely the gross structure of the organ which makes it highly susceptible to the effects of rejection is not clear. The second type of operation/

operation involves taking a sole pancreatic graft, partial or total from a donor and reconstructing a vascular supply in the groin of the recipient using the iliac vessels (Bergan 65, Tiexera 66 and 67, Kelly 67, Merkel 68, Reemtsma 68, Gliedman 73). The advantages of this procedure are easier technique and the avoidance of problems with transplanted bowel. However, drainage of the exocrine pancreas presents some difficulties. Some workers believe that failure to drain the exocrine secretions contributes to the pancreatitis which always accompanies grafting, and may severely compromise the survival of the organ. In addition, when the duct is merely divided and tied, there is a strong potential for continued exocrine leakage from the gland, and in the immunosuppressed patient, the presence of protein-rich fluid makes infection likely. Methods of drainage have therefore been devised, including external cutaneous fistulae (Reemtsma 68) and pancreatic duct-duodenum anastomoses which appear to work satisfactorily. On the other hand, some authors consider that duct ligation is sufficient (Brynger 75, Tiexera 67); no controlled trial has yet been done to determine which approach is the more rational.

Grafting techniques always include a period of time when the organ has no blood supply, and the pancreas is no exception. Preservation between removal and implantation is usually possible using low temperatures, and the pancreas has been kept alive for up to 24 hours using both continuous hypothermic albumin perfusion and simple hypothermia (Brynger 75).

When a pancreas is transplanted, restoration of endocrine function is prompt; blood glucose is often normal within 24 hours (Sabiston 68) and both insulin and glucagon are secreted by the graft (Brynger 75). In many cases, transient hypoglycaemia is seen in the first post-operative day (Bergan 65, Idezuki 68, Merkel 68, Reemtsma 68) associated with hyperinsulinaemia (Lillehei 70), but the reason for this is not understood. It was suggested that if pancreatic venous blood was directed into the I.V.C, hormonal degradation would be reduced owing to by-pass of the liver (Bergan 65). However, a study involving orthotopic and heterotopic allografting showed that there was no significant difference in glucose metabolism between pancreatic venous return directed into the systemic or portal systems (Idezuki 68). The most likely explanation is transient, reversible ischaemia to the islet cells suffered during the transfer. Hyperglycaemia does not occur until rejection of the pancreas commences (Bergan 65) and the glucose tolerance curve and insulin response to glucose stimulation remain normal until this time (Lillehei 70).

Seemingly, then, carbohydrate metabolism is well controlled by the/

the transplanted organ, but what of the long-term diabetic complications? The literature is not extensive on this aspect but in streptozotocin diabetic rats, pancreatic transplantation was shown to halt the development of nephropathy, although there was no evidence of reversal of pre-existent lesions (Weil 74) and a human study showed that retinal haemorrhages and visual acuity problems regressed after transplantation, although microangiopathic retinopathy did not change in long-term survivors (Gliedman 73). This indicates that although autoregulatory stabilisation of carbohydrate metabolism may arrest or delay the development of complications, actual disappearance of the lesions is unlikely. However, some hope may be offered by the recently reported regression of a Kimmelstiel-Wilson body in a diabetic kidney grafted into a non-diabetic recipient (Barker 75), but this unfortunately does not exclude the possibility that the basic defect causing nephropathy remains after pancreatic transplantation.

As in all allografting procedures, the most formidable problem is rejection. In the early stages the pancreas becomes grossly oedematous, indurated, and shows interstitial bleeding which in the latter stages develops into a full-blown haemorrhagic necrosis (Lillehei 70). Histologically, the process is characterised by a mononuclear infiltrate which spares the islet tissue until late on (Bergan 65), and even in the final stages of chronic rejection, when the acinar tissue is almost completely replaced by fibrous tissue, islet cells can still be distinguished (Lillehei 70). This suggests that islet cells are less antigenic than other tissue and certainly some work indicates that the pancreas may be immunologically privileged. When kidney and bowel are transplanted along with the pancreas, much greater difficulties arise with rejection of the former two organs (Gliedman 73). Indeed, in a series of 10 human patients where pancreas grafting accompanied kidney transplantation, there had been no evidence of pancreatic rejection although only two of the subjects were alive at the time of publication (Lillehei 70). In addition, acinar atrophy of the grafted pancreas in dogs, brought about by prior duct ligation, improved the success rate of the operation by 40% (Reemtsma 68).

One conclusion to be drawn from the above information is that the pancreas as a whole is less antigenic than most tissues and that the islet cells are even more privileged than the exocrine tissue. However, using isolated pancreatic islets, it has recently been shown that in rats, at least, the endocrine portion of the pancreas is unequivocally as vulnerable to rejection as other tissues (Reckard 73). How then do we explain the good results obtained in experimental and clinical grafting? My contention is that the pancreas is not immunologically privileged but that it may be less susceptible to damage by rejection because of its relatively simple, homogenous structure when compared to the bowel or kidney. It is also possible that the exocrine portion somehow protects the endocrine cells from the invading lymphocytes, and this is worth bearing/

bearing in mind when considering the transplantation of isolated islets.

If rejection of an organ is to be adequately and promptly treated, some easily measurable indication of impending gross dysfunction is necessary. Hyperglycaemia is the obvious choice with the pancreas (Bergan 65)(Tiexera 66), but it must be remembered that the use of steroids in immunosuppression will have a hyperglycaemic effect itself, and hence minor disturbances of carbohydrate metabolism cannot be adduced as evidence of rejection (Largiadier 67). Provocative tests, especially the intravenous OGTT, have been successfully employed in predicting rejection before the process has advanced (De Jode 66, Idezuki 68, Largiadier 67, Lillehei 70), and amylase levels have also proved useful (Tiexera 67). It should be noted, however, that the duct ligated pancreas gives rise to a permanent hyperamylasaemia (Tiexera 67) and thus negates the usefulness of the latter test. Rejection must be distinguished from thrombosis, another major cause of failure in the grafted pancreas, and this has been achieved using arteriography (Lillehei 70).

Having considered detection of rejection, let us now turn to its treatment. In most cases, standard therapy with azathioprine and steroids is applied, and in humans this is the same regime as is used for the renal transplantation which is usually done concurrently. In dogs it was found that heterologous antilymphocyte serum alone was a potent immunosuppressive agent (Merkle 68) and this has been used as an adjunct to the more conventional treatment in human subjects (Lillehei 70).

The concept of transplanting isolated islets was instituted because it was thought initially that these cells might be minimally antigenic, and the technique was made possible by the development of a simple method of separating intact islets from the pancreas (Lacy 67). As we have seen, the immune privilege theory has been largely discredited, but the method may still prove useful as it involves less trauma and fewer gross complications than transplantation of the pancreas itself. A major problem in this field is to find the best site for depositing the transplanted cells. Intraperitoneal islets certainly induce normoglycaemia in streptozotocin-diabetic rats (Reckard 73), but it has recently been demonstrated that intra-portal administration is superior as it minimises the required dosage and gives a longer-term cure without recurrence (Reckard 74). The reason for this is not clear; portal insulin is no more effective in lowering blood sugar than other routes, and intraportal islets are no less immunogenic than intraperitoneal - immunosuppression must be used in both cases/

cases to achieve prolonged results. It is possible that better vascularisation of islets occurs in the liver than in the peritoneal cavity. Human islet transplantation has been carried out in one patient already immunosuppressed for kidney grafting - the patient received 3 doses of islets from 3 different donors, each dose being about 7% of the normal pancreatic content, but although this decreased insulin requirement, prolonged function was not obtained (Barker 74). Owing to the low yield of the separation technique, islet cell availability is a formidable problem, but a new method for cultivating human islet cells has been described (Lawson 74) and may provide part of the answer.

So the human experience with isolated islets is not encouraging - but what of pancreatic transplantation in general - is it a useful mode of therapy? A number of attempts at human grafting have been carried out (Kelly 67, Brynger 75, Lollehei 70, Gliedman 73, Johnston 68, Calne 75) but most of these have been done in patients with terminal renal disease, who were immunosuppressed anyway for kidney transplants. In one study it was found that a staged transplantation of pancreas with subsequent renal allografting had a better prognosis than the synchronous operation (Gliedman 73). It was suggested that poor renal function was due to an immunological cross reaction with the pancreas, but the series was small and it seems equally possible that the longer more extensive operation may have compromised kidney function.

The results are not impressive, but they are encouraging, and a recent survey gives the following:

Number of pancreatic transplants	- 36
Number alive with functioning grafts	- 1
Longest current survival with functioning graft	- 2 years.

(Calne 75)

It must be remembered that these operations were not done under ideal conditions and, even so, carbohydrate metabolism was uniformly controlled in all patients until rejection set in, and in most cases renal rejection was more severe than pancreatic.

In conclusion, it would seem that pancreatic transplantation may offer the best hope for juvenile-onset diabetics as it provides an autoregulatory system for insulin replacement, which may control the development of long-term complications better than discreet injections of the hormone. However, we must end on a cautionary note. In a recent statement issued by the National Institute of Arthritis, Metabolism and Digestive Disease and endorsed by the American Diabetic Association, it was warned that success in total or subtotal transplantation of the pancreas has been "exceedingly limited" and should not be regarded as a form of treatment of diabetes but as a highly experimental procedure (Special Report 74). It should again be stressed that most transplants are done on kidney recipients who are immunosuppressed anyway; the long-term effectiveness of pancreatic transplantation is/

is not yet substantiated and, at present, the inconvenience of immunosuppression is greater than that of conventional diabetic therapy. Another important consideration is whether transplanted islet cell tissue will eventually be affected by the disease; it must be remembered that in experimental animals the diabetes is the result of mere islet cell deficiency obtained by alloxan, streptozotocin or surgical ablation, whereas the disease itself may well have a systemic cellular or humoral defect as its basis. Finally, the lesions which develop in these experimental animals are assumed to be similar to human diabetic complications and to have the same aetiology, but this need not be so. Despite these objections, however, if it transpires that pancreatic transplantation is effective in controlling the sequelae of diabetes mellitus, then it may be deemed justifiable to risk the rigours of immunosuppression in an attempt to obtain successful pancreatic grafting in the early stages of the disease. Hopefully, improved methods of combating rejection and more accurate histocompatibility typing will reinforce efforts in this direction.

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